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Original Article

Nasal mupirocin treatment of pharynx-colonized methicillin resistant *Staphylococcus aureus*: Preliminary study with 10 carrier infants

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Abstract

Background: Nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection in infants has become a serious concern and a new means of preventing the transmission of MRSA in the community needs to be considered.

Methods: We performed nasal mupirocin treatment on 10 infants who were MRSA-positive either in the nose or the pharynx and evaluated the effect of mupirocin on the eradication of MRSA.

Results: Eradication of MRSA from the nose was successful in two cases and eradication from the pharynx in six (66.6%) of nine cases. The number of treatments required to achieve eradication varied; within three courses for nose carriers and from one to seven courses for pharynx carriers. Eradication was unsuccessful even after five to seven treatments in three pharynx-limited carriers.

Conclusions: These data suggest that the effect of nasal mupirocin treatment on pharynx-colonized MRSA is limited and that repetitive treatment is necessary in some cases. However, in view of the possibility of preferential pharyngeal colonization of *Staphylococcus aureus* in infancy, nasal mupirocin treatment deserves further evaluation for eradication not only of nose- but also of pharynx-colonized MRSA.

Key words infant, methicillin resistant *Staphylococcus aureus*, mupirocin, pharyngeal colonization.

Recently, neonatal nosocomial infection with methicillin-resistant *Staphylococcus aureus* (MRSA) has become a serious concern. We experienced an outbreak of exfoliative toxin A (ETA)-producing MRSA infection in our neonatal nursery between June and October 1996. During this time we performed epidemiologic and bacteriologic analysis and found that 29 out of 123 normal neonates (23.6%) were positive for MRSA and that 16 of the MRSA-positive neonates (55.2%) had ETA-related symptoms,[1] such as impetigo and conjunctivitis, with the same MRSA found from the lesion. Although previous reports have shown that MRSA colonized in neonates disappears within 6 months to 1 year after birth,[2,3] our epidemiologic follow-up survey showed that 12 of 28 MRSA-positive cases (42.9%) still remained MRSA positive 10 months after the outbreak and MRSA in these cases caused relapse and secondary infection.[4] Moreover, in contrast to the general notion that the nasal cavity is the site of colonization, the MRSA in our cases colonized preferentially at the pharynx.[5] It colonized only in the pharynx in nine patients, only in the nose in one and at both sites in one (Table 1). We do not know whether this is a common characteristic of MRSA or specific to our isolates. However, Hurst reported in 1957 that hospital-acquired *Staphylococcus aureus* in babies persisted in their throats longer than in their noses,[6] suggesting that preferential pharyngeal colonization in infants is a common tendency of *Staphylococcus aureus*. In view of the possibility of preferential pharyngeal colonization, a means of eradicating MRSA not only in the nose but also in the pharynx should be developed in order to prevent MRSA transmission in the community. In this respect, we were interested in the effect of nasal mupirocin treatment, which is commonly used to eradicate MRSA in the nasal cavity, on eradication of pharynx-colonized MRSA.

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Methods

Staphylococcus aureus resistant to methicillin and ceftizoxime, as determined by SHOWA DISK® (Showa Yakuhin Kako, Tokyo, Japan), was defined as MRSA. All the MRSA in the present study were coagulase type III, as

Table 1 Colonization of MRSA and nasal mupirocin treatment

No.	Name	Sex	Colonization		ETA-related symptoms		No. treatments	Eradication by treatment	Susceptibility to mupirocin	
			Nose	Pharynx	Within 1 month	Relapse			BT	AT
1	HY	M	–	+	–	–	1	DO	ND	ND
2	TT	M	–	+	+	–	1	O	ND	ND
3	MM	M	–	+	+	–	7	X	3 +	3 +
4	MH	M	–	+	+	+ †	1	O	ND	ND
5	OK	M	–	+	+	–	5	X	3 +	3 +
6	KY	F	–	+	+	+ ‡	3	O	ND	ND
7	NF	F	–	+	–	–	5	X	3 +	3 +
8	OS	M	–	+	–	–	5	O	ND	ND
9	MS	M	–	+	–	–	7	O	ND	ND
10	YY	M	+	–	–	–	3	O	ND	ND
11	MK	M	+	+	+	+ §	7	O	ND	ND
12	YR*	F	–	ND	+	+ **	ND	ND	ND	ND

*Fecal culture positive for methicillin-resistant *Staphylococcus aureus* (MRSA). Relapse occurred after †4, ‡2, §9 or **8 months. ETA, exfoliative toxin A; BT, before treatment; AT, after treatment; M, male; F, female; DO, dropped out; ND, not done; O, successful; X, unsuccessful.

determined by rabbit anticoagulase serum (Denka Seiken, Tokyo, Japan), and the presence of the *mecA* and *ETA* genes were confirmed by gene analysis using the polymerase chain reaction (PCR) as described by Hayakawa *et al*.[1]

Nasal treatment with mupirocin was performed in 10 of 12 MRSA-positive infants between August 1997 (approximately 10 months after the outbreak) and February 1998, at the pediatric outpatient clinic in Kyoto National Hospital. Details of the profiles of these 12 carrier infants are shown in Table 1. All the infants were born at the hospital as normal full-term babies with a birthweight of more than 2500 g. Seven of the babies showed ETA-related symptoms, such as impetigo and conjunctivitis, in their neonatal period. Furthermore, four of the seven babies showed relapse of symptoms during a 10-month follow-up period (Table 1). The same MRSA was found from the lesions.

Informed consent was obtained from all of the mothers, who performed the mupirocin treatment at home after the doctor had provided an adequate explanation of the procedure. On the basis of the supplier's recommendation, one course of treatment was defined as an application of mupirocin to both sides of the nasal cavity three times per day for 3 consecutive days. One week after the course, nasal and pharyngeal cultures were taken. Culture samples were obtained by rubbing the inner part of the pharynx or both sides of the nasal cavity extensively (approximately 10 s for each sample) using sterilized swabs. The collection of the samples was performed by the same doctor throughout the study. If MRSA still existed in either culture, the same course was repeated, followed by further nasal and pharyngeal cultures. A maximum of 5–7 courses were performed on each patient. Eradication of MRSA was defined as more than two consecutive negative cultures of both nasal and pharyngeal swabs after treatment.

Susceptibility of MRSA to mupirocin was investigated qualitatively, using MUPIROCIN SHOWA DISK® (Showa Yakuhin Kako). Briefly, $1–2 \times 10^4$ c.f.u./cm^2 of isolated MRSA was cultured on Nissui agar medium for drug sensitivity disc (Nissui, Tokyo, Japan) at 35°C for 24 h. The MRSA was judged as being sensitive to mupirocin if the inhibition diameter was greater than 12 mm.

Results

Eradication of MRSA was successful in five of eight pharynx-limited carriers and in one nose-limited carrier, but failed in three pharynx-limited carriers. In case 11 (pharynx and nose carrier), eradication was successful in both the nose and the pharynx. Overall, MRSA was eradicated from the nose in each of two cases and from the pharynx in six out of nine cases (66.6%).

Nose-colonized MRSA was eradicated within three courses in both cases (one course for case 10 and three for case 11 in Table 1). However, the number of treatments required for eradication of pharynx-colonized MRSA varied, one course in two cases, three in one case, five in one case and seven in two cases (Table 1). In another three cases (cases 3, 5 and 7 in Table 1), MRSA remained positive even after 5–7 courses of treatment. The susceptibility to mupirocin of the treatment-resistant MRSA from these three carriers was tested before and after treatment. Although MRSA remained even after repetitive treatment with mupirocin, no MRSA was found to be mupirocin-resistant after treatment (Table 1).

Discussion

Although mupirocin is commonly used to eradicate MRSA in the nasal cavity,[7] few data have been reported as to the effect of nasal mupirocin treatment on MRSA colonized in the pharynx, where it is difficult to eradicate. This is especially the case with infants, because they cannot gargle with disinfectants. We do not think that all MRSA acquired at hospital should be eradicated, even after discharge. On the contrary, we think that if the MRSA did not produce any toxins and was harmless, we should wait for its natural elimination. However, during a 10-month follow-up period, we experienced a relapse of symptoms (either impetigo or conjunctivitis) in four cases (cases 4, 6, 11 and 12) and secondary infection (impetigo) among family members in one case (case 7).[4] We therefore thought that active eradication was needed for this harmful type of ETA-producing MRSA. Although the number of subjects is small, we think that the data are still valuable because the prevalence of this harmful MRSA, which requires active eradication among infants, is a rare experience.

Our study was the first attempt to eradicate MRSA colonized specifically in the pharynx with the use of mupirocin in the nasal cavities. It was thought that a high enough concentration of mupirocin could reach the pharynx through the nasal cavities, although we did not prove the presence of mupirocin in pharyngeal swabs. Nakamura *et al*.[8] showed, in a study at their neonatal intensive care unit (NICU), that nasal mupirocin treatment was very effective and eradicaiton of all MRSA was successful, not only from the nose, but also from the pharynx within three courses of treatment. Contrary to their findings, we found that the mupirocin was only partially effective in our study, so that eradication of MRSA was achieved in only six of the nine (66.6%) pharynx carriers. Moreover, more than five courses were necessary in three of the six successful cases and eradication was not achieved in another three cases despite their having 5–7 repetitive treatments. Several differences may explain this discrepancy: (i) Nakamura *et al*. treated high-risk neonates in the NICU, while we treated 10-month-old, otherwise normal infants; and (ii) in the case of Nakamura *et al.*, most of the MRSA was found both in the pharynx and the nose, suggesting that the MRSA in the pharynx was not originally colonized in the pharynx but passed from the nose, while most of our MRSA was found specifically in the pharynx. Whatever the reason, our data, combined with those of Nakamura *et al*.,[8] suggest that pharynx-colonized MRSA in late infancy may be more difficult to eradicate by nasal mupirocin treatment than in neonates.

Mupirocin is a dose-dependent drug and the emergence of mupirocin-resistant MRSA has been reported recently.[9–11] The use of mupirocin as a skin ointment has been reported to induce high resistance in infancy.[11] Because dilution of the drug during the passage from the nasal cavity to the pharynx may induce drug resistance, we stopped the mupirocin treatment after 5–7 courses, regardless of whether eradication was accomplished or not. Resistance to mupirocin has been reported when a total of 150 g is used as a skin ointment.[11] In our study, the total amount of mupirocin used was only 3–6 g, so the remaining MRSA was still susceptible to the drug. Although our method can be performed safely, drug susceptibility must be checked periodically if longer mupirocin treatment is to be performed.

In summary, we showed that, although nasal mupirocin treatment was at least partially effective in the eradication of pharynx-colonized MRSA, repetitive treatment is necessary in some cases. Although the data are preliminary due to the small number of subjects, they still indicate that pharyngeal culture should be included in the study of MRSA colonization and that nasal mupirocin treatment should be further evaluated as a means of eradication of pharynx-colonized MRSA, in view of the possibility of preferential pharyngeal colonization of *Staphylococcus aureus* in infancy.

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